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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,491	12/27/2001	Shuyuan Zhang	29853/37706	9920

7590 07/13/2005

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,491	ZHANG ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-226* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-226* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.o d

DETAILED ACTION

Applicant's response, amendments, and co-submitted declaration of 4/11/05 have been entered.

Claims 70-72, 101-102, 132-133, 163-164, and 194-195 have been amended.

Claims 70-226 are pending and considered.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-226 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12 and 31 of U.S. Patent No. 6,726,907 for reasons of record.

Response to Argument – Double Patenting, 6,726,907

Applicant's response and arguments of 4/11/05 have been fully considered but are not found persuasive.

Applicant argues that the claimed subject matter of U.S. Patent No. 6,726,907 (the adenoviral compositions) is patentably distinct from the therapeutic methods presently claimed, and thus the obviousness-type double patenting should be withdrawn (Applicant's argument of 4/11/05, p. 22, paragraph 4).

Such is not persuasive. The claimed adenoviral compositions of the patent have only one disclosed use: therapy (e.g., col. 5, last paragraph-col. 6, paragraph 3); and as such, the Artisan would have found it obvious, from the compositions, to apply such compositions to effect a known successful gene therapy treatment. Moreover, the Examiner has reviewed the Application file of U.S. Patent No. 6,726,907 and has not found the present subject matter to have been restricted out in such Application file. However, the Application file does not appear to contain all of the papers in the case; therefore, if Applicant can supply evidence that such subject matter was restricted, the Examiner would remove the rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-226 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31, and 33-37 of copending Application No. 09/203,078, for reasons of record.

Double-Patenting over 09/203,078 held in Abeyance

In accord with Applicant's request, the provisional double-patenting rejection over U.S. Application No. 09/203,078 is maintained, but held in abeyance (Applicant's response of 4/11/05, p. 22, paragraph 5).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-226 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-89 of U.S. Patent No. 6,194,191. Although the conflicting claims are not identical, they are not patentably distinct from each other

because the instant Application's claims are drawn to methods of therapy requiring administration of adenoviral vectors prepared by the same methods as U.S. Patent No. 6,194,191. Moreover, the specifications of the Application and the Patent are the same, with only use for the adenoviral vectors manufactured in the Patent: gene therapy (e.g., col. 5, last paragraph-col. 6, paragraph 3).

Hence, from U.S. Patent No. 6,194,191, it would have been obvious to utilize the same vectors prepared in the patent to effect a known gene therapy. The Artisan would have been motivated to do so because such is the purpose of preparing such vectors in the patent. Moreover, the Artisan would have had a reasonable expectation of success, because the patent demonstrates that such adenoviruses could be made, and the art contains various instances where such gene therapy with adenovirus vectors is successful.

Lastly, it is noted by the Examiner that the present subject was not found to be restricted out in the Application file of U.S. Patent No. 6,194,191. Hence, the rejection is proper.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's amendments and arguments, the rejections of Claims 70-226 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

Claim Rejections - 35 USC § 112 – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of the amendments and arguments, the rejections of claims 70-226 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn on the basis of "any promoter" and "any therapeutic gene"; however, Claims 70-226 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for "a therapeutic adenovirus", for reasons of record.

Response to Argument – Written Description

Applicant's arguments of 4/11/05 have been fully considered, but are not found persuasive.

Applicant argues that the many species of adenovirus, comprising genes, driven by promoters, are provided, and hence, the genera of any therapeutic adenovirus was possessed by Applicant at the time of invention (Applicant's argument of 4/11/05, p. 24, last paragraph).

Such is not persuasive. As is indirectly recognized by Applicant, no adenovirus that is therapeutic in and of itself, is possessed by Applicant (Official Action of 10/6/04, sentence bridging paragraphs 7-8; Applicant's response of 4/11/05, p. 24, last paragraph), and Applicant's broad claims do not require the presence of a transgene and promoter element. Hence, the written description rejection is proper.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-226 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of treating a patient for a tumor, comprising the art-recognized form of administration of the adenoviral vector encoding p53 operably linked to a promoter and other expression control elements for expression in the tumor cells, which vector is prepared by a method comprising growing cells in a medium, providing nutrients, infection of the cells with the adenovirus vector, lysing the cells, purifying the adenovirus, and formulating such purified adenovirus,

does not reasonably provide enablement for treating any disease/disorder in any animal by administering any adenoviral vector comprising any transgene, yields of adenovirus that are 70% +/- 10% of that found in the lysate by any other method than growing the cells at a low to medium perfusion rate of 1-2 g/L glucose, followed by detergent lysis with 1% Tween 20, a single anion exchange chromatography step in a Toyopearl Super Q 650 FPLC anion exchange column, and concentration/diafiltration and nuclease treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for reasons of record and reasons newly-applied.

For purposes of clarity, and in order to maintain a clear record, the rejection is repeated below, along with the new bases provided.

Background

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention, and that, therefore, Applicant's claims are not enabled.

The Breadth of the Claims

Claims 70-226 are broad in scope. The following paragraphs will outline the breadth of these claims.

Independent Claims 70, 101, 132, 163, and 194 encompass a method of treating a patient with any therpeutic adenovirus composition, comprising obtaining a therapeutic adenovirus

compoisition that has been prepared by a process that comprises growing host cells in media, providing nutrients to the host cells, infecting the host cells with any adenovirus, lysing the host cells, purifying the adenovirus from the lysate, formulating a therapeutic adenovirus composition, and administering the composition by any method to any patient. Claim 101 requires the growing of host cells to be in a bioreactor or on a microcarrier. Claim 132 requires the nutrients to be provided by perfusion or fed-batch or roller-bottle processes. Claim 163 requires the purification to be by any process than freeze-thaw. Claim 194 requires the purification to include a chromatography step, without the use of CsCl.

Dependent Claims 71-100, 102-131, 133-162, 164-193, and 195-226, which depend from 70, 101, 132, 163, and 194, respectively, include further alterations to the steps of obtaining an adenovirus composition, the incorporation of transgenes, promoters, and specific transgenes and promoters (it is noted that the present invention is considered only with respect to CMV-MIE promoter and the p53 transgene). However, for purposes of this rejection, these alterations of the steps of obtaining an adenoviral composition are immaterial, as the specification does not provide any reason to believe these compositions are materially distinct from those adenoviral compositions obtained from other methods.

Further, specific claims require virus product yield, relative to the amounts present at lysis, to be 70% +/- 10%, which can be obtained by any method.

Hence, because these claims encompass the treatment of any patient with any adenoviral vector or adenoviral vectors, and any method of obtaining the specific amounts of viral yield, the specification must flesh-out a wide area of knowledge, to a reasonable extent, so that one of skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would able to practice

the invention, and do so to its fully claimed scope, without an undue burden being imposed on such Artisan. Undue burden is typically found when the Artisan would have to perform large amounts of experimentation to find the working embodiments of Applicant's claimed invention, essentially amounting to the Artisan "inventing" the claimed invention himself or herself. As will be shown below the breadth of Applicant's claims (or that portion of the claims considered, specifically), is large enough to provide for a series of unpredictabilities that the Artisan would have to overcome with respect to the vast majority of embodiments to which the claims are considered.

The Nature of the Invention

The nature of the invention is gene therapy, i.e., the use of vectors to genetically transform cells, and thereby treat a patient. The very nature of gene therapy is not generally enabling of new inventions in the field. The general nature of the invention has been this way for many years. The following paragraphs provide an eloquent analysis of the general nature of gene therapy. Although some of these articles date back over the past eight years, they are utilized because they provide a succinct and eloquent analysis of gene therapy, and the difficulties and unpredictabilities have still not been overcome by the art, as will be shown in the state of the prior art (next section), even though many more articles are published each month.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at

adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy

(e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Lastly, with regard to adenoviruses without specific transgenes and promoters, no art of record demonstrates how such adenoviruses could effect treatment of any disease.

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing to reasonable predict that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, would overcome this showing for that specific method of administration to that specific species, because, if treatment is successful, it must have met these aforementioned requirements.

With regard to the specific amounts of yield of virus, relative to the amounts present at time of cell lysis, it is clear in the art that such specific yields will depend on the exact steps used in any particular method of isolation. For Example, Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, demonstrates that even for a particular method, yields and purity will vary widely between specific experiments (p. 1411, col. 1, paragraph 1). Hence, the Artisan would not be

able to reasonably predict, absent more information, whether any particular technique will produce any particular level of yield.

The State of the Prior Art

The prior art is similarly not generally enabling for new inventions in the field of gene therapy and the treatment of cancers with adenoviral vectors. The reasons are the same as that of the nature of the invention, as well as other unpredictabilities peculiar to this specific art.

Green, et al. (2002) Cancer Gene Therapy, 9 : 1036-42 provides a general overview of the treatment of cancers with adenoviral vectors.

The first issue which Green presents is one of targeting and of administration route: "The development of a targeted adenoviral vector, which can be delivered systemically, is one of the major challenges facing cancer gene therapy." (ABSTRACT). Moreover, clearance issues abound in the art too, "The virus is readily cleared from the bloodstream, can be neutralized by pre-existing antibodies, and has permissive cellular tropism." Lastly, although Applicant's specification does not describe adenoviral vectors without transgenes that can treat cancer, Green describes conditionally-replicating adenoviruses, e.g., ONYX, which have, "shown limited efficacy, but there are several hurdles to overcome to achieve an effective tumor-specific system therapy." (Id.). In this abstract, Green has systemically demonstrated that there exist many unpredictabilities in the field, which echo that of the general nature of gene therapy: targeting, clearance, and tissue specificity.

With regard to actual treatments, mice being treated have similarly shown problems with delivery, due to clearance through the liver and preexisting immunity, which can cause the death of mice before any treatment could be effected (p. 1037, col. 1, paragraphs 2-3).

With regard to conditionally replicating vectors, a few approaches have been used, but these approaches are similarly not generally enabling of new inventions in the field. Specifically, the inhibition of p53 may be used to effect selective replication of adenoviral vectors (it is noted that this is in direct contrast the elected p53 gene, so those embodiments considered with regard to p53 would not be efficacious in this method). Moreover, several reports demonstrate that tumor-selective adenoviral vectors can replicate in wild-type p53-containing cells (p. 1038, col. 2, last paragraph). Other approaches use tissue-specific promoters to effect replication in particular tissue types (p. 1039, paragraph bridging columns). However, Applicant's specification has not even contemplated this approach, as they only discuss placing the essential genes of adenoviral replication under the control of a packing cell line, and not for the control of a specific tissue (e.g., p. 40, last paragraph).

Moreover, neither Green's publication, nor Applicant's specification, nor in any art of record, are any mutant forms of p53 described which would be efficacious in any form of treatment. Hence, the Artisan would not be able to reasonably predict that any form of p53 could be used. (Such is discussed in further detail in the analysis of Applicant's provided guidance and direction.)

Green finishes the discussion with a listing of some key hurdles to overcome for effective gene therapy with adenoviral vectors and cancer, including problems with liver uptake, neutralizing antibodies, and the use of genes other than p53 for treating cancer (p. 1040, whole page).

From Green it is clear that the Artisan would not be able to reasonably predict that any method of administration would be efficacious for treating cancer with any adenoviral vector,

particularly p53-encoding adenoviruses, because of problems with targeting, clearance and efficacy.

On the other hand, U.S. Patent 6,740,320 to Zhang, et al., filed 2 June 1995, patented 25 May 2004, describes the use of p53-encoding adenoviruses for treating cancer in animals comprising the direct administration of such vectors to the cancer (ABSTRACT). Zhang teaches the direct administration of such vectors (e.g., col. 16, lines 39-48).

Moreover, no art of record teaches the treatment of anything other than cancer with p53 expressing cells or selectively replicating cells.

Hence, although the art, in view of the nature of the invention, is generally enabling for particular already established treatments with adenoviral vectors encoding a transgene, the art is not enabling for treating any patient, for any disease or disorder, by any administration, by any route, of any adenoviral vector. The reasons that the art, in view of the nature of gene therapy, raises a number of unpredictabilities such that the artisan would not be able to predict that any particular claimed embodiment would be efficacious. These unpredictabilities include: whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment and whether immune responses would kill the patient before therapy could be effected.

To further elaborate on the lack of enablement provided by the art with regard to any gene therapy, it is recognized that the art at the time of filing recognizes various specific therapies, requiring specific transgenes, in specific methods of treatment, which perhaps finds its

most predictable use in treatment of cancer and angiogenesis. However, Applicant's claim does not only encompass these embodiments, but embraces both the predictable and unpredictable therapies. To wit, Applicant's adenoviral vectors at the time of filing, were not reasonably predictable for treatment of, for example, brain diseases. For evidence, Applicant is directed to Peltekian, et al. (1997) J. Neurosci. Meths. 71: 77-84. Peltekian reviews the use of adenoviruses for gene transfer to treat various neurological diseases (TITLE; ABSTRACT). In the article, Peltekian recognizes that these vectors **may** be appropriate for brain diseases, e.g., Huntington's disease, Parkinson's disease, epilepsy, or multiple sclerosis, "**once both the vector and the gene of interest have been defined and optimized**" (ABSTRACT). Such problems include cell type specificity (i.e., targeting) (p. 78); can the vector spread widely into the brain (i.e., tareting) (p. 79); the length time the tissue remains transduced (i.e., producing enough mRNA and protein therefrom for a long enough time) (p. 79); and immune rejection (i.e., cells may be destroyed before therapy can be effected) (p. 80). Hence, because the genus meant to be encompassed is generic, to cover all gene therapy techniques, the subject matter which is claimed is not patentable under 35 USC 112, first paragraph. Lastly, Applicant is directed to the section labeled "The Amount of Direction and Guidance Provided by Applicant" (BELOW, this Action). As is shown in that section, Applicant has only specifically contemplated the application of p53-encoded transgenes, and while listing many other genes, such genes are not linked to specific diseases, and as such it would constitute undue experimentation to determine which genes, by which methods would provide an efficacious effect. In effect, this is because Applicant's disclosure does not evidence possession of treating "any disease known to be treatable by adenoviral vectors. Because of such lack of possession, Applicant lacks enablement.

Therefore, the level of disclosure by Applicant, by way of specific guidance and direction, and/or example, would be required to provide enough information for the artisan to overcome the unpredictabilities discussed above. However, as will be shown, such disclosure has not been provided.

With regard to the lack of reasonable predictability for yields of virus particles with any particular method of isolation, no art of record overcomes the lack of reasonable predictability evidenced in the nature of the invention. In fact, logic tells that it cannot. Each type of purification step is inherently different from any other, and the specific levels of purity depend not only on the what is being purified, but what else is in the mixture, and the material and method of the step. For example, Perrin also demonstrates yields for different method steps of isolation (TABLE 1), which yields vary greatly. Hence, it is not reasonably predictable whether a particular level of yield will be obtained given any particular method of isolation, and, moreover growth conditions, as such would inherently alter the composition used in the method.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed to its fully-claimed scope without undue experimentation.

The Level of Predictability in the Art

Because the art, as shown above, does not disclose enough to reasonably predict whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target

sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment and whether immune responses would kill the patient before therapy could be effected, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in any particular therapeutic application. Moreover, because it is not reasonably predictable whether any particular method step of isolation or growth will yield any particular level of virus particle, absent more information, the Artisan could not predict that such levels of yield could be obtained by any particular method.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for its fully claimed scope.

The Amount of Direction and Guidance Provided by Applicant

The specification broadly discusses methods of the production and purification of adenoviruses (pp. 2-8), broad discussion of uses of adenoviral vectors and their preparation (pp. 11-12), host cells for the growing of adenoviruses (pp. 12-14), growth of such cells and vectors in selection media (pp. 14-16), cell culture systems (pp. 17-28), methods of harvesting cell lysates (pp. 29-36), concentration and filtration of adenoviruses from lysates (pp. 37-38), viral infection for obtaining suitable viruses (pp. 38-43), engineering viral vectors with genes (pp. 43-48),antisense constructs (pp. 48-50), and antigens for vaccines (p. 50). Further broad discussion is given for promoters, enhancers, and polyA tails (pp. 50-57), methods of gene transfer (pp. 57-

60), the removal of nucleic acid contaminants (pp. 60-61), and viral purification (pp. 61-72), pharmaceutical compositions (pp. 72-75).

Furthermore, specifically, with regard to the methods of isolation, Applicant makes clear that the method of the invention is based on the cellocube bioreactor, with low to medium perfusion rates, with lysis by detergent, and further having a single ion exchange run, with concentration/diafiltration, to obtain the unexpected yield of 70% +/- 10%, which is further advantageously better than ultracentrifugation (pp. 11-12, paragraph bridging). Moreover, the specification makes clear that such rates are limited to a low to medium perfusion rate of 1-2 g/L perfusion of glucose (EXAMPLE 2). Lysis is employed with 1% Tween-20 (EXAMPLE 3). Lastly, the virus is isolated by column chromatography on a Toyopearly Super Q 650M FPLC anion exhange column (EXAMPLE 6). Hence, due to the lack of reasonable predictability in the art, as well as Applicant's specific acknowledgement that the particular method of growth and isolation is important to the invention, other methods of isolation are not reasonably predictable to produce the levels of purity required.

Moreover, from the specification and the state of the prior art, the Artisan would not able to reasonably predict that any p53 gene would produce efficacious protein for Applicant's invention. As noted in the analysis of the prior art, Green, nor any Art of record, describes any working mutant forms of p53 (discussed with regard to Green, in the state of the prior art). Furthermore, Applicant discusses p53 on pages 43-45 of the Specification, stating that "Wild-type p53 is recognized as an important growth regulator in many types of cells" (p. 44, line 16). Also, Applicant cites a number of mutations that produce non-functioning p53, i.e., contributes to uncontrolled cell growth, and only provides wild-type p53 in the context of arresting

uncontrolled cellular growth (pp. 43-45). Hence, because the majority of mutant p53 forms produce uncontrolled cellular growth, the Artisan would not be able to reasonably predict that any form of p53 would be able to inhibit cellular growth, except wild type p53.

With regard to the use of such adenoviral vectors to any disease, Applicant's disclosure specifically recognizes the use of p53-encoding transgenes for treatment of cancer (pp. 43-45, lists many other genes that presumably are indicated to be involved in various cancers (pp. 45-46), and a laundry list of various enzymes and proteins (pp. 46-47), as well as broad disclosure of various diseases (pp. 47-48). However, none of these genes are specifically linked to any particular disease, and hence, the Artisan would not be able to reasonably predict which genes to use, through which methods, for the treatment of any particular genes. Such lack of disclosure is considered to amount to a lack of enabling disclosure, as the Artisan would not know which genes to use in which diseases, and would not even know if Applicant contemplated any particular gene and disease combination, in any particular method.

However, such broad discussion does not provide the specific direction and guidance the Artisan would require to reasonably predict whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment and whether immune responses would kill the patient before therapy could be effected, and whether any particular form of p53 except wild-type would be efficacious, for any particular embodiment. Therefore, absent a strong showing by way of

specific example, it would have required undue experimentation to make and/or use the invention within the full scope of the invention, as claimed by Applicant.

The Existence of Working Examples

Example 1 describes the general materials and methods used, and it is noted that only a single adenoviral vector is used in the examples: AdCMVp53 (Applicant's elected species of promoter and transgene). Example 2 demonstrates the effect of perfusion rate on virus production and purification, using Applicant's Cellcube™ system. Example 3 demonstrates methods of harvesting and lysis of vectors. Example 4 demonstrates the effect of concentration/diafiltration on virus recovery. Example 5 demonstrates the effect of salt addition on Benzonase treatment. Example 6 demonstrates ion exchange chromatographic purification of adenoviral vectors. Example 7 demonstrates other purification methods. Example 8 demonstrates AdCMVp53 purification from crude virus generated in Applicant's Cellcube™ system. Example 9 demonstrates improved AD-p53 production in serum-free suspension culture.

However, none of these examples demonstrate a single therapeutic treatment. They also do not overcome any single unpredictability in the art. Hence, even after reviewing Applicant's specification, the Artisan would not be able to reasonably predict, for any particular embodiment, whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment.

With regard to the amounts of yield required, how the experiments relate to the analysis is given within the amount of direction and guidance provided, because the two issues are tied closely together (see above).

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the lack of pertinent working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, the Artisan would have been required to perform a large amount of experimentation to make and/or use the invention within its fully-claimed scope.

Such experimentation would be required to reasonably predict whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment, whether any particular form of p53 except wild-type would be efficacious, and whether immune responses would kill the patient before therapy could be effected. Further experimentation would be required to determine the particular steps of growth and purification required to obtain 70% +/- 10% yields of virus particle.

Conclusion

Because of the large amount of experimentation required to make and/or use the invention within the full scope of each claim, as claimed by Applicant, such experimentation is considered undue, and therefore, the claims are not enabled for any treatment other than p53 with

cancer, or for obtaining any specific level of viral yield. Applicant is advised to consult the first paragraph for a more specific listing of what is, and what is not, enabled.

Response to Argument – Enablement

Applicant's response of 4/11/05 has been fully considered but is not found persuasive.

Applicant argues that the Examiner has provided no reasoning why any form of gene therapy could not be effected, and as such, the claims are enabled (Applicant's argument of 4/11/05, p. 26, paragraph 2)

Such is not persuasive. The Examiner has provided ample reasoning and evidence why not any form of gene therapy would be reasonably predicted to be efficacious. Such is again reiterated above, and was supplied in the enablement of the previous Official Action of 10/6/04. Applicant is urged to read such rejections. Moreover, specific instances include the sections labeled "Nature of the Invention" and "State of the Prior Art".

Applicant argues that the claims are enabled for more than treating cancer with a p53 gene (Applicant's argument of 4/11/05, p. 26, paragraph 3).

Such is persuasive. Hence, the Examiner has widened the scope of enablement to cover gene therapies known to be successful with adenoviral vectors.

Applicant argues that the references in the Nature of the Invention only generalize about gene therapy, that they do not state the therapy would not work, and they focus on clinical aspects of gene therapy, which are not the standards the office applies in determining enablement (Applicant's argument of 4/11/05, p. 26, last paragraph).

Such is not persuasive. The Examiner fails to understand how, e.g., targeting, expression of enough mRNA and protein therefrom for a long enough period of time, in enough cells, to

effect therapy is strictly clinical (See Nature of the Invention, above and in the Official Action of 10/6/04).

Applicant argues that p53 gene therapy for cancer is enabled, and that the issues in the Nature of the Invention do not Apply (Applicant's argument of 4/11/05, p. 27, paragraphs 2-6).

Such is persuasive, but misplaced. Applicant's claims were found enabled for gene therapy of cancer, but not for any form of gene therapy with adenoviral vectors (See Official Action of 10/6/04, enablement rejection; also See Above).

Applicant supplies further references to argue other forms of therapy are enabled; however such is not required, as Applicant's present enablement is to any gene therapy already known effective with adenovirus (Applicant's argument of 4/11/05, p. 27-28, paragraph bridging).

Applicant supplies a long review of the breadth of methods of administration, genes, preparations, and formulations taught by the specification, and as such, Applicant argues sufficient guidance is given for any gene therapy with the adenoviruses (Applicant's argument of 4/11/05, pp. 28-31).

Such is not persuasive. While listing the various compositions and methods certainly evinces that Applicant considered using a particular route and gene, but unless that form of therapy was already known in the art, Applicant is not enabled for it. Such is, as is reviewed above, because it would be undue experimentation to determine the various embodiments that would be efficacious (See ABOVE). Moreover, the sheer number of genes provided does not entitle applicant to any disease. As acknowledged, some gene therapies with adenoviral vectors do work on a limited scale. However, Applicant's claims are to any therapy under the sun, e.g.,

claim 70, and the working embodiments encompassed under this whole genera still are not reasonably predictable; moreover, Applicant's claims are not limited to therapies already known effective.

Applicant cites various clinical trial evidence, and MPEP 2107.03 IV, to argue that the bountiful evidence of various clinical trials enables the full scope of the claims (Applicant's argument of 4/11/05, p. 31, last paragraph).

Such is not persuasive, and irrelevant. First, Applicant's cited section of the MPEP is directed to utility, not enablement. Second, Applicant's enablement is limited to known effective gene therapy methods, not to only p53 for cancer gene therapy. Hence, known effective gene therapy, including those under clinical trial, are enabled.

Applicant further supplies a declaration by Dr. Menander declaring that various clinical trials are underway, and as such the claims are enabled (Declaration of 4/11/05 by Dr. Menander).

Such is not persuasive. While such clinical trials are indicative of utility, the evidence still does not indicate that these methods are reasonably predictable for treatment in the variety of diseases, disorders, genes and animal species encompassed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

> has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

In light of Applicant's amendments and arguments, the rejections of Claims 72, 74, 89-82, 84 and 101-226 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, are withdrawn; however:

Claims 70-71, 73, 75-77, 83, and 85-100 remain rejected under 35 U.S.C. 102(e) as being anticipated by Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416. (Note: Although this rejection now cites a new art reference, such reference is merely used in support of the inherency of the methods of Zhang, and hence, this rejection is not considered a new rejection.)

With regard to Claims 70-71, 97, and 100, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.).

With regard to Claim 73, Zhang teaches the use of cesium chloride gradients in the purification of the adenovirus. Moreover, Applicant indicates that such levels of contamination are a result of cesium chloride gradient isolation (e.g., Applicant's SPECIFICATION, TABLE 10). Therefore, Zhang inherently attains the level of contamination required.

With regard to Claims 85-90, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 91-93, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 94-95, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 98-99, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences

these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1).

With regard to claim 71, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 75-77, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 83, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claim 96, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2).

Response to Argument – Zhang, anticipation

Applicant's argument of 4/11/05 has been fully considered but is not found persuasive.

Applicant argues that the various steps are not taught by Zhang, and as such the claims are not anticipated.

Such is not persuasive for the reasons evidenced by Huyghe, above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In light of Applicant's amendment and arguments, the rejections of Claims 73-74, 77, 104-105, 108, 135-136, 139, 166-167, 170, 197-198, and 201 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002 and U.S. Patent No. 5,837,520 to Shabram, et al, filed 7 March 1995, Patented 17 November 1998, are withdrawn.

Claim Rejections - 35 USC § 103

Claims 70, 78-82, and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416 as applied to claim 70 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50.

As shown above, Zhang, as evidenced by Huyghe, teaches the various aspects of claim 70, however, Zhang does not teach the aspects of BSA levels below the detection limit of western blots, serum free media, bioreactors, microcarriers, or perfusion methods.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Claim Rejections - 35 USC § 103

Claim 74 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416 and Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe, teaches the various aspects of claim 70; however, Zhang does not teach or make obvious the aspect of nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such

ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Claim Rejections - 35 USC § 103

Claims 101, 103-104, and 106-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416 as applied to claims 70-71, 73, 75-77, 83, and 85-100 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50.

As shown above, Zhang, as evidenced by Huyghe, teaches the various aspects of claims 71, 73, 75-77, 83, and 85-100; however, Zhang does not teach the aspects of bioreactors and/or microcarriers, BSA levels below the detection limit of western blots, serum free media, bioreactors, microcarriers, or perfusion methods.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant

teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Claim Rejections - 35 USC § 103

Claims 132, 134-135, and 137-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and Perrin, et al. (1995) Vaccine, 13(13): 1244-50.

With regard to Claims 132, 134, 159 and 162, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.).

With regard to Claim 135, Zhang teaches the use of cesium chloride gradients in the purification of the adenovirus. Moreover, Applicant indicates that such levels of contamination are a result of cesium chloride gradient isolation (e.g., Applicant's SPECIFICATION, TABLE 10). Therefore, Zhang inherently attains the level of contamination required.

With regard to Claims 147-152, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 153-155, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 156-157, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 160-161, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are

inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1).

With regard to claim 134, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 137-139, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 145, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claim 158, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2).

However, Zhang does not teach the aspects of perfusion, roller bottles, BSA levels below western blot detection levels; serum free media; bioreactors; or microcarriers.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Claim Rejections - 35 USC § 103

Claim 105 is rejected under 35 U.S.C. 103(a) as being unpatentable over over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50 as applied to claim 101 above, and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe and further in view of Perrin, makes obvious the various aspects of claim 101; however, Zhang does not teach or make obvious the aspect of nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Claim Rejections - 35 USC § 103

Claims 163, 165-166, 168-170, 176, and 178-193 rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and in view of Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128.

With regard to Claims 163, 165, 190, and 193, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells

(e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.).

With regard to Claim 166, Zhang teaches the use of cesium chloride gradients in the purification of the adenovirus. Moreover, Applicant indicates that such levels of contamination are a result of cesium chloride gradient isolation (e.g., Applicant's SPECIFICATION, TABLE 10). Therefore, Zhang inherently attains the level of contamination required.

With regard to Claims 178-183, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 184-186, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 187-188, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 191-192, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media,

providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1).

With regard to claim 165, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 166 and 168-169, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 176, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claim 189, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2).

However, Zhang does not teach the aspect of lysing the cells containing the adenovirus by a method other than free-thaw methods.

On the other hand, Graham teaches that it is known in the art to use 5% sodium deoxycholate, which disrupts the cells without disrupting the virions (e.g., p. 119, paragraph 1).

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the cell disruption technique of Graham. The Artisan would have been motivated to do so because such methods disrupts the cells without disrupting the virions. Moreover, the Aritsan would have had a reasonable expectation of success, because Zhang had already grown the virions, and Graham had demonstrated that it was known in the art to lyse the cells by such technique.

Claim Rejections - 35 USC § 103

Claims 171-175 and 177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128 as applied to claim 163 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50.

As shown above, Zhang and Graham obviate the limitations of claim 163, as further evidenced by Huyghe; however, they do not teach or suggest the aspects of bioreactors and/or microcarriers, BSA levels below the detection limit of western blots, serum free media, bioreactors, microcarriers, or perfusion methods.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant

teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang and Graham with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Claim Rejections - 35 USC § 103

Claim 167 is rejected under 35 U.S.C. 103(a) as being unpatentable Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and in view of Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128, and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe and further in view of Graham, makes obvious the various aspects of claim 163; however, Zhang does not teach or make obvious the aspect of nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such

ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Claim Rejections - 35 USC § 103

Claims 194, 196-197, 199-201, and 199-201, 207, and 209-226 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further evidenced by Huyghe.

With regard to Claims 194, 196, 221, and 224, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.).

With regard to Claim 197, Zhang teaches the use of cesium chloride gradients in the purification of the adenovirus. Moreover, Applicant indicates that such levels of contamination are a result of cesium chloride gradient isolation (e.g., Applicant's SPECIFICATION, TABLE 10). Therefore, Zhang inherently attains the level of contamination required.

With regard to Claims 209-214, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 215-217, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 218-219, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 222-223, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are

inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1).

With regard to claim 196, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 199-201, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 207, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claim 220, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2).

With regard to claims 225-226, Huyghe teaches the use of a single anion-exchange chromatography steps (p. 1405, col. 2, paragraph 3-p. 1406, paragraph 2) for isolation.

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Huyghe. The Artisan would have been motivated to do so because such alternative steps were known, standard protocols in the art. Moreover, the Artisan would have had a reasonable expectation of success, because Zhang had taught the methods of treatment, and Huyghe had demonstrated the methods to be successful in isolating the virus particles.

Claim Rejections - 35 USC § 103

Claims 194, 202-206, and 208 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further evidenced by Huyghe, as applied to claim 194 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50.

As demonstrated above, Zhang and Huyghe obviate the limitations of claim 194, however, they do not teach or suggest the aspects of BSA levels below the level of western blot detection, serum free media, bioreactors, microcarriers, perfusion techniques, or roller bottles.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang and Huyghe with the steps of Perrin. The Artisan would have been motivated to do so

because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Claim Rejections - 35 USC § 103

Claim 198 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further evidenced by Huyghe, and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe, makes obvious the various aspects of claim 194; however, Zhang does not teach or make obvious the aspect of nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying

adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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